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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/035,324	01/04/2002	H. William Bosch	029318-0107	2223

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EXAMINER	
HAGHIGHATIAN, MINA	
ART UNIT	PAPER NUMBER
1616	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/035,324	BOSCH ET AL.	
	Examiner	Art Unit	
	Mina Haghighatian	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 November 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,9-11 and 13-37* is/are pending in the application.

4a) Of the above claim(s) *15-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7, 9-11, 13-14, 35-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/22/10*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114 was filed in this application after a decision by the Board of Patent Appeals and Interferences, but before the filing of a Notice of Appeal to the Court of Appeals for the Federal Circuit or the commencement of a civil action. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 11/22/10 has been entered.

Receipt is acknowledged of the Amendments, Remarks and an IDS filed on 11/22/10. Claims 1 and 35-37 have been amended, no claims have been cancelled or newly added. Claims 15-34 remain withdrawn. Accordingly, claims **1-7, 9-11, 13-14 and 35-37** remain under examination.

NOTE: The pending claims are substantially the same as claims that have been at least twice rejected, and AFIRMED by the Board of Patent Appeals and Interferences on 09/28/2010. Although appropriate rejection would have been a FINAL rejection, the rejection is made non-final to give Applicants an opportunity to file further amendments,

data and/or supporting documents (Per Applicant's request, See Statement of Interview filed on 11/05/10).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-7, 9-11, 13-14 and 35-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wiedmann et al (5,747,001) in view of Desai et al (US 20070117862) and as evidenced by Verrecchia (6,139,870).

Wiedmann et al teach aerosols containing droplets of an aqueous **dispersion** of nanoparticles of **insoluble beclomethasone** particles having a surface modifier on the surface thereof. Representative examples of surface modifiers include gelatin,

benzalkonium chloride, PVA, sorbitans, etc (see col. 3, line 30 to col. 4, line 45). A suitable surfactant is **tyloxapol** (see col. 4, lines 49-60), the particles are preferably less than 400 nm in size, or more preferably less than 250 and most preferably **less than 100 nm** in size (see col. 6, lines 8-15 and col. 10, lines 25-35). The process of making such nanoparticles includes attrition and **filtration** (see col. 7, lines 18-21). It is disclosed that the concentration of the beclomethasone in the liquid medium can vary from about 0.1 to 60%, and preferably from 5-30% (w/w) (see col. 6, lines 19-22). Wiedmann discloses that the surface modifiers can be present in the formulation in an amount from 0.1-90% or preferably from 20-60% based on the total weight of the dry particles (see col. 6, lines 23-28 and col. 10, lines 40-55). Wiedmann discloses filtration, but lacks teachings on sterile filtration.

Desai et al teach formulations for in vivo delivery of pharmacological agents in which the pharmacologically active agent is delivered in the form of suspended particles. There is also provided, a process of preparing unusually small **nanoparticles** of less than 200 nm in diameter, which can be **sterile-filtered**, through a 0.22 micron filter (see [0051]). Desai et al disclose methods for the preparation of substantially water insoluble pharmacologically active agents for in vivo delivery, said method comprising, combining an organic solvent having said active agent dissolved therein, water, a surfactant and a co-surfactant that spontaneously form a micro-emulsion and removing said organic solvent to yield a suspension of nanoparticles of said active agent in said water (see [0093] to [[0100]). It is further disclosed that insoluble active agents include

inhalant corticosteroids such as beclomethasone dipropionate and budesonide (see [0122] and [0146]).

Examples **4, 5 and 8** disclose a nanoparticle formation wherein the dispersion is sterile filtered.

Verrecchia discloses that "It has now been found, and this forms the subject of the present invention, that particles can be prepared, 95% of which have an average diameter of less than 100 nm, and more specifically have an average diameter of between 20 and 75 nm, and which can thus be subjected to a sterile filtration on 0.22 um filters without a loss in yield. These particles are moreover more stable than those which could be obtained according to the prior art and can be lyophilized without leading to any phenomenon of particle agglomeration" (see col. 1, lines 26-35). Verrecchia also discloses that "the nanoparticles thus obtained may be filtered without giving rise to problems of caking together and in good yields" (see col. 2, lines 53-57).

All sterile filtered formulations are expected to be free of contaminants. Thus the newly added limitation of "free from biological contaminants" is met.

With regards to the limitation "consisting of" in claim 35, Wiedmann teaches that the nanoparticles can be surface modified with any of the listed surface modifying agents such as polymers, Tween™, tyloxapol, casein, gelatin, celluloses, dextran, lecithin, etc (see col. 3). Desai also teaches that nanoparticles surface modifies with a stabilizing agents such as proteins are suitable. Desai also recites that a number of

biocompatible polymers can be used in the formation of said particles such as dextrans, celluloses, starch, alginates, lipoproteins, etc (see e.g. [0174]). Thus, the claims would have been obvious because the substitution of one known element for another would have **yielded predictable results** to one of ordinary skill in the art at the time of the invention.

With regard to new claims 36-37, the claims are written in a product-by-process format. According to MPEP 2113 [R-1], product-by-process claims are not limited to the manipulations of the recited steps, only the structure implied by the steps. Therefore, claims 36-37 are taught by the cited references.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to have implemented the sterile filtration method as taught by Desai et al in the formulations and process of Wiedmann, since Wiedmann teaches filtration of nanoparticles of beclomethasone and tyloxapol. Thus, one of ordinary skill in the art would have been motivated to implement sterile filtration of Desai et al instead of simple filtration of Wiedmann because sterilized formulations are safer and beneficial to recipients. In other words, the claims would have been obvious because the technique for improving a particular product was part of the ordinary skill in the art, in view of the teaching of the technique for improvement in other situations. Specifically, it is shown that sterile filtration of solid dispersions of nanoparticles in liquid mediums is known in the art (as taught by Desai et al). Weidmann teaches the formulations.

Claims 1-7, 9-11, 13-14 and 35-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wood et al (WO 9625918) in view of Desai et al (US 20070117862) and as evidenced by Verrecchia (6,139,870).

Wood et al teach aerosols containing droplets of an aqueous **dispersion** of nanoparticles of **insoluble beclomethasone** particles having a surface modifier on the surface thereof. Representative examples of surface modifiers include gelatin, benzalkonium chloride, PVA, sorbitans, etc (see pages 6-7). A suitable surfactant is **tyloxapol** (see page 8). The particles are preferably less than 400 nm in size, or more preferably less than 250 and most preferably **less than 100 nm** in size (see page 16). The process of making such nanoparticles includes attrition and **filtration.** It is disclosed that the concentration of the beclomethasone in the liquid medium can vary from about 0.1 to 60%, and preferably from 5-30% (w/w) (see examples). Wood et al discloses that the surface modifiers can be present in the formulation in an amount from 0.1-90% or preferably from 20-60% based on the total weight of the dry particles. Wood et al discloses filtration, but lacks teachings on sterile filtration.

Desai et al, discussed above, teaches sterile filtration of dispersions of nanoparticles.

All sterile filtered formulations are expected to be free of contaminants. Thus the newly added limitation of "free from biological contaminants" is met.

With regards to the limitation "consisting of" in claim 35, Wood et al teaches that the nanoparticles can be surface modified with any of the listed surface modifying agents such as polymers, Tween™, tyloxapol, casein, gelatin, celluloses, dextran, lecithin, etc (see cols. 4-5). Desai also teaches that nanoparticles surface modifies with a stabilizing agents such as proteins are suitable. Desai also recites that a number of biocompatible polymers can be used in the formation of said particles such as dextrans, celluloses, starch, alginates, lipoproteins, etc (see e.g. [0174]). Thus, the claims would have been obvious because the substitution of one known element for another would have **yielded predictable results** to one of ordinary skill in the art at the time of the invention.

With regard to new claims 36-37, the claims are written in a product-by-process format. According to MPEP 2113 [R-1], product-by-process claims are not limited to the manipulations of the recited steps, only the structure implied by the steps. Therefore, claims 36-37 are taught by the cited references.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to have implemented the sterile filtration method as taught by Desai et al in the formulations and process of Wood et al, since Wood et al teach filtration of nanoparticles of beclomethasone and tyloxapol. In other words, one of ordinary skill in the art would have been motivated to implement sterile filtration of Desai et al instead of simple filtration of Wood because sterilized formulations are safer and beneficial to recipients. In other words, the claims would have been obvious because the technique

for improving a particular product was part of the ordinary skill in the art, in view of the teaching of the technique for improvement in other situations. Specifically, it is shown that sterile filtration of solid dispersions of nanoparticles in liquid mediums is known in the art (as taught by Desai et al). Wood et al teaches the formulations.

Response to Arguments

Applicant's arguments filed 11/22/10 have been fully considered but they are not persuasive.

Applicant argues that "In the Decision on Appeal, the Board asserts that the claim language does not distinguish the particles of the claimed invention from those of Verrecchia. Applicants have amended the claims to explicitly recite that the claimed composition comprises solid nanoparticulate beclomethasone particles, solid nanoparticulate budesonide particles, or a combination thereof, and a liquid dispersion medium. Accordingly, it is not obvious to sterilize the claimed composition which is a dispersion comprising solid particles by filtering it through a 0.2 micron filter in view of Verrecchia's teaching of filtering an emulsion comprising two immiscible liquids" (see Remarks, page 12).

This is not found persuasive because Wiedmann et al and Wood et al specifically disclose insoluble beclmethasone and budesoinde particles being dispersed. On the other hand, Verrecchia teaches sterile filtering suspensions of hydrophobic and water-insoluble nanoparticles. Both Desai and Verrecchia teach sterile filtration of dispersions

of nanoparticles without specifically using the term solid. However it is implied that dispersions of nanoparticles includes solids as well.

Furthermore, Verracchia specifically disclose that the "nanoparticles according to the invention are advantageous on account of their stability. This stability makes it possible, in particular, to obtain a lyophilizate of good quality whose redissolution and/or resuspension, during use is improved and for which the reconstituted suspension contains particles similar in diameter to that of the initial nanoparticles" (see col. 3, lines 10-16). According to medical dictionary (found at http://medical-dictionary.thefreedictionary.com/lyophilization) lyophilization is "The process of isolating a **solid** substance from solution by freezing the solution and vaporizing the ice away under vacuum conditions". Thus, by definition, Verrecchia's nanoparticles are SOLID.

It has clearly been shown that, all that is missing from Wiedmann et al or wood et al is sterile filtration. It has also been shown that sterile filtration (liquids and solids) of nanoparticles is well known in the art. As Desai et al and Verrecchia teach sterile filtration of dispersions of nanoparticles that are stabilized using stabilizers.

Claims 1-7, 9-11, 13-14 and 35-37 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mina Haghighatian whose telephone number is (571)272-0615. The examiner can normally be reached on core office hours.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Mina Haghighatian/

Mina Haghighatian
Primary Examiner
Art Unit 1616